



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/SE97/01122</p> <p>(22) International Filing Date: 19 June 1997 (19.06.97)</p> <p>(30) Priority Data: <u>9602644-8</u> <u>4 July 1996 (04.07.96)</u> SE</p> <p>(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): JENSFELT, Birgitta [SE/SE]; Essinge Högväg 44, S-112 65 Stockholm (SE).</p> <p>(74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: NEW USE OF A HYDROGEL FORMULATION</p> <p>(57) Abstract</p> <p>Use of a hydrogel formulation consisting essentially of (i) one or more gelling agents; (ii) water; (iii) optionally a pH-adjusting agent; (iv) optionally a plasticizer; and (v) optionally a surfactant; for the manufacture of a medicament for the treatment of distal inflammatory bowel diseases, in particular for the rectal treatment of ulcerative colitis. This novel use is advantageous in that no local anaesthetics or other active ingredients are required in order to achieve satisfactory relief upon treatment.</p>		

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NEW USE OF A HYDROGEL FORMULATION

Field of the invention

5 The present invention relates to the use of a hydrogel formulation for the treatment of distal inflammatory bowel diseases, and particularly for the rectal treatment of ulcerative colitis.

Background of the invention and prior art

10 Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology. The disease is characterized by inflammation of the mucosa of the colon, along with crypt abscesses and ulcers, and almost always involves the rectum.

15 Various drugs have been used to treat the above described disease. Examples of such drugs known from the prior art are sulfasalazine, corticosteroids and immunosuppressants. However, the drawback with the use of such prior art compounds are that they often give undesired side-effects in the CNS area as well as in the gastrointestinal area, and failure to
20 respond to the treatment is common (see e.g. *Inflammatory Bowel Diseases, 1992, Corona AB, Astra, Malmö, Sweden, the following chapters: a) 5-aminosalicylic acids and 4-aminosalicylic acids based drugs in the treatment of inflammatory disease, Gunnar Järneroth; b) Corticosteroids, S.B. Hanauer; and c) Immunosuppressive therapy in inflamed bowel disease, H.R. Dayton, D.P. Jewell*). Approximately 5 % of the patients that
25 today require treatment cannot be treated with sulfasalazine because of hypersensitivity. Another 5-10 % of the patients show severe gastrointestinal side-effects. A further drawback is that long-term treatment is required for satisfactory improvement. Most of the patients suffer from recurrent symptoms, and treatment has to be initiated again.

Thus, the problem underlying the present invention was to find a new and further improved way of treating distal inflammatory bowel disease, and in particularly ulcerative colitis.

The use of local anaesthetics for the treatment of mucosal inflammation is known from
5 US 5,331,013.

Outline of the invention

10 It has now surprisingly been found that the rectal administration of a hydrogel formulation as described more fully below, provides an improvement in the treatment of distal inflammatory bowel diseases, and in particularly in the rectal treatment of ulcerative colitis. Rectal administration of such a hydrogel formulation is effective in the treatment of distal inflammatory bowel diseases, particularly in the treatment of ulcerative colitis, without the
15 need for also a local anaesthetic as active ingredient, which is advantageous from a side-effect point of view.

The hydrogel formulation which is prepared in accordance with the present invention comprises the use of the following ingredients:

20

- (i) One or more gelling agents;
- (ii) water;
- (iii) optionally a pH-adjusting agent;
- (iv) optionally a plasticizer; and
- 25 (v) optionally a surfactant.

Any pharmaceutically acceptable gelling agent which is non-toxic is useful in accordance with the present invention.

30

Preferred gelling agents are hydroxypropyl methylcellulose, Carbopol[®], i.e. carbomer 934P (MF18), pectin, sodium carboxymethylcellulose, agar or a combination thereof.

- 5 The amount of gelling agent and water in the hydrogel composition according to the present invention, depends on the choice of gelling agent. Thus, gelling agents should be used in amounts suitable for the purpose of being applicable in form of a gel.

- 10 Agents adjusting the pH may be chosen from any acid or base which are pharmaceutically acceptable and non-toxic. The pH of the colon of human beings varies between different humans, but lies within the approximate pH range 4.0 - 7.0. Therefore, the pH of the hydrogel composition according to the present invention is preferably within the range 4.0 - 7.0.

- 15 The use of a hydrogel composition as defined above, provides an anti-inflammatory effect in particularly on ulcerative colitis upon rectal administration.

20 Pharmaceutical compositions

- The hydrogel composition according to the present invention is prepared by mixing one or more gelling agents with water while stirring, and optionally adding any other ingredient in different ways depending on the choice of gelling agent. The final
25 weight of the composition is adjusted with purified water, and the pH-value is adjusted with a suitable acid and/or base to a suitable pH-value.

- Alternatively the gelling agent(s) is/are mixed with water, and the mixture is allowed to swell at a low stirring rate over night. Thereafter any other ingredients are added, and the
30 final weight of the composition is adjusted.

The hydrogel composition thus achieved, is preferably filled into a syringe or vial which thereafter is sealed and finally sterilized by a standard autoclaving cycle and stored at room temperature. The product achieved is a syringe or vial filled with a hydrogel composition of the present invention, ready to use.

5

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

10

Example 1

	Hydroxypropyl methylcellulose 4000 cps	2.45 g
15	Hydrochloric acid 2M for injection	q.s.
	Purified water for injection	up to a total weight of 100 g

The hydroxypropyl methylcellulose was mixed with warm (80 °C) purified water while stirring. When the gel had cooled to room temperature, the pH was measured and adjusted with acid to pH 4.0-7.0. The final weight of the gel was adjusted with purified water.

The final composition had a pH value of 5.7.

20

Example 2

	Hydroxypropyl methylcellulose 4000 cps	2.45 g
	Hydrochloric acid 2M for injection	q.s.
5	Purified water for injection	up to a total weight of 100 g

The hydroxypropyl methylcellulose was mixed with warm (80 °C) purified water while stirring. When the gel had cooled to room temperature, the pH was measured and adjusted with acid to pH 4.0-7.0. The final weight of the gel was adjusted with purified water.

10 The final composition had a pH value of 4.2.

Example 3

	Hydroxypropyl methylcellulose 4000 cps	2.45 g
15	Sodium hydroxide 2 M for injection	q.s.
	Purified water for injection	up to a total weight of 100 g

The hydroxypropyl methylcellulose was mixed with warm (80 °C) purified water while stirring. When the gel had cooled to room temperature, the pH was measured and adjusted with acid to pH 4.0-7.0. The final weight of the gel was adjusted with purified water.

20 The final composition had a pH value of 6.7.

Example 4

25	Carbopol 934P	0.2 g
	Propylene glycol	0.2 g
	Tween [®] 20	7 mg
	Purified water for injection	up to a total weight of 100 g

Carbopol 934P was mixed with purified water at 70 °C. The dispersion was allowed to swell at a low stirring rate over night. Propylene glycol and Tween[®] 20 were added, and the final weight was adjusted with water at room temperature.

5

Example 5

Pectin	6 g
Purified water	up to a total weight of 100 g

10

The pectin was mixed with warm purified water while stirring. When the gel had cooled to room temperature, the pH was measured and the final weight was adjusted with purified water. The final composition had a pH of 4.5.

15

Example 6

Sodium carboxymethyl cellulose (high viscous)	2 g
Hydrochloric acid 2 M	q.s. to pH 4.0-7.0
Purified water	up to a total weight of 100 g

20

The sodium carboxymethylcellulose was mixed with warm (80 °C) purified water while stirring. When the gel had cooled to room temperature, the pH was measured and adjusted with acid. The final weight of the gel was adjusted with purified water.

25 The final composition had a pH of 5.1.

Example 7

	Agar	0.7 g
5	Purified water	up to a total weight of 100 g

The agar was mixed with 10 g purified water while stirring. The rest of the water was heated to 100 °C and added to the mixture. The mixture was boiled for 2 minutes. The final weight was adjusted with warm purified water and the mixture was sieved. When the gel
10 had cooled to room temperature, the pH was measured. The final composition had a pH of 6.9.

BIOLOGICAL EVALUATION15 Model A

Intrarectal administration of trinitrobenzenesulfonic acid induced a colitis-like inflammation in the rat distal colon. Rats were treated once daily with a hydrogel composition of the invention (0.2 ml) during one week. Muscle contractions in response to
20 various stimuli decreased in the inflamed rats. The contractile responses of rats treated with a hydrogel composition of the invention, increased back to normal values.

Trinitrobenzene-induced colitis

25 Rats received an intrarectal injection of 0.6 ml trinitrobenzenesulfonic acid and 0.25 ml 50 % ethanol. Treatment with a hydrogel composition of the invention started 24 hours after the induction. Rats were treated once daily with a hydrogel composition of the invention (0.2 ml) during one week.

Measurement of contraction

Colonic segments from the distal part were placed in 5 ml chambers containing Kreb's bicarbonate solution maintained at 37 °C, and gassed with 95 % O₂ and 5 % CO₂ giving a pH of 7.4. Thereafter the segments were placed under an initial tension of 9.81 mN and equilibrated for 60 min with repeated washings with Kreb's solution before experiments were undertaken. Isometric contraction was measured using a Grass FT03C force displacement transducer operating a Grass Polygraph.

10

Experimental design

The amplitude of the dominant phasic contraction in response to acetylcholine (ACh), electrical field stimulation, serotonin (5-HT) and substance P which is a peptide well known to a person skilled in the art, was measured and expressed as a percentage of the maximally effective phasic contraction in response to ACh (10⁻³ M). Contraction-response curves were constructed by addition of single doses of the substance studied, followed by repeated washings until basal muscle tension was retained.

20

Statistical analysis

Contractile responses were expressed as a percentage of the maximal responses to ACh (10⁻³ M). Values are given as means of 6-10 experiments. Statistical significance was evaluated using Kruskal-Wallis test followed by Mann-Whitney (posthoc) test.

25

Results

Acetylcholine, serotonin and substance P caused concentration-dependent contractions
 5 whereas electrical field stimulation resulted in frequency-dependent contractions of the
 colonic segments. The contractions of inflamed colonic segments of normal colon in
 response to ACh, 5-HT and electrical field stimulation decreased compared to the
 responses in normal colonic segments. The treatment with a hydrogel composition of the
 present invention resulted in increased contractile responses compared to the inflamed
 10 colon segments, however not significant in all cases.

The results are shown in Table 1 below, where also data for a hydrogel composition
 containing the local anaesthetic ropivacaine is included for comparative purposes.

15 Table 1

Acetyl choline (μ M)	Normal colon	Inflamed colon	Colon treated with the hydrogel of Example 1	Colon treated with hydrogel containing ropivacaine
0.1	13.5	0.8	0.0	6.7
1	25.3	5.5	16.4	28.0
10	42.8	12.4	41.9	73.6
100	71.3	18.1	62.3	89.3
1000	100.0	24.6	94.1	73.7

A value of 100.0 is the reference value for a normal colon. Thus, as shown in Table 1
 above, a colon treated with a hydrogel composition of the present invention showed a

reduced inflammation giving a value of 94.1, approaching the value for a normal colon having a value of 100.0.

HUMAN TESTS

5

The following study was performed on patients suffering from ulcerative colitis.

The treatment lasted for 6 weeks. Endoscopy for the assessment of mucosal inflammation was performed prior to treatment and after 2, 4 and 6 weeks of treatment. The extent of the
10 disease was recorded at study entry as well as upon termination of treatment.

Biopsies from the colonorectal mucosa, to determine the severity of inflammation, were sampled at study entry and at treatment termination.

15 Remission

After 6 weeks of treatment, there was no significant difference between the treatment groups where the patients had been treated with a hydrogel of the present invention and groups where patients had been treated with a hydrogel composition containing also the
20 local anaesthetic ropivacaine.

Table 2 shows the percentage of treated patients in remission after 6 weeks treatment with a hydrogel composition of the present invention. For comparative purposes Table 2 also shows the percentage of remission for patients which were treated with a hydrogel
25 composition containing also the local anaesthetic ropivacaine in a concentration of 50, 100 and 150 mg respectively.

Table 2

Hydrogel composition	No. of patients	Week 2	Week 4	Week 6
Hydrogel of Example 1	47	8.5	14.9	27.7
and 50 mg ropivacaine	47	6.4	12.8	23.4
and 100 mg ropivacaine	48	4.2	22.9	31.2
and 150 mg ropivacaine	43	7.0	34.9	32.6

5 As is shown in Table 2 above, there was no significant difference between treatment groups treated with a hydrogel composition containing also ropivacaine in as high concentration as 150 mg, and treatment groups treated with a hydrogel without any local anaesthetic.

10 After 4 weeks of treatment, the p-value is 0.011 (ITT) and 0.023 (PP) for the difference between a hydrogel containing 150 mg ropivacaine and a hydrogel without any local anaesthetic.

The patients in remission after this treatment period of 6 weeks, did not require any further
15 treatment.

Improvement

20 After 6 weeks of treatment, there was no significant difference ($p=0.105$), in the intention to treat analysis, between the treatment groups where the patients had been treated with a hydrogel of the present invention and groups where patients had been treated with a hydrogel composition containing also the local anaesthetic ropivacaine in an amount of 150 mg. In the per protocol analysis the difference between a hydrogel composition containing

also ropivacaine in an amount of 150 mg and a hydrogel composition without any ropivacaine, was not statistically significant after 6 weeks.

Table 3 shows the percentage of the treated patients which showed an improvement after 6 weeks treatment with a hydrogel composition of the invention. For comparative purposes Table 3 also shows the percentage of improvement for patients which were treated with a hydrogel composition containing also the local anaesthetic ropivacaine in a concentration of 50, 100 and 150 mg respectively.

Table 3

Group	No. of patients	Week 2	Week 4	Week 6
Hydrogel of Example 1	47	51.1	57.4	59.6
and 50 mg ropivacaine	47	40.4	51.1	63.8
and 100 mg ropivacaine	48	52.1	66.7	66.7
and 150 mg ropivacaine	43	69.8	74.4	76.7

Model B

Animals

Male rats (Sprague-Dawley, B&K Universal), weighing 215-220 g and fed *ad libitum*, were used.

Experimental colitis

Experimental colitis was induced using the method described by Morris et al. Rats fasted for 12 hours were anaesthetised with Hypnorm (0.1 ml i.m.) and an infant feeding tube was inserted rectally into the colon so that the tip was 8 cm proximal to the anus, approximately at the splenic flexure. Thereafter, 0.85 ml of a mixture of trinitrobenzenesulphonic acid (5 % w/v, TNB; Sigma) dissolved in 0.25 ml 50 % ethanol was instilled into the lumen of the colon. The installation procedure required 5 seconds to complete. Finally, 0.5 ml air was injected to clear completely the TNB/ethanol solution from the cannula, and the anaesthetised animals were kept for a few minutes in a supine Trendelenburg position.

Experimental design

TNB/ethanol colitis was induced in 40 rats. Animals were thereafter randomised into 4 therapeutic groups to receive daily therapy from day 1 (24 hours after induction of colitis).

Assessment of colonic damage and inflammation

After one week of treatment, the rats were anaesthetised with metofane and the distal colon (10 cm) was removed. The severity of colitis was assessed by macroscopic evaluation.

Macroscopic assessment

The macroscopic assessment of colonic damage examined the presence of oedema, hyperemia, dilatation, exfoliated epithelium and necrosis. Furthermore, the presence or absence of adhesions between the colon and other organs were noted as well as the presence or absence of diarrhoea. Finally, signs of healing mucosa in the colon was recorded. The results are shown in Table 4.

Table 4

Type of Hydrogel	No. of animals	Damage score
Control=TNB	10	61.5
Example 5	10	44.0
Example 6	10	44.5
Example 7	10	25.5 ^a

^a p=0.0007

Intracolonic administration of TNB/ethanol resulted in extensive inflammation of the distal colon with severe oedema, hyperaemia, dilatation, exfoliated epithelium and necrosis. The damage induced by TNB was also characterized by severe diarrhoea and fibrinous adhesions to the small bowel (and other organs). The total number of colonic damage signs were added up to for each group. The macroscopic damage evaluated after one week of treatment was reduced, as seen in Table 4. The incidence of adhesion formations between the distal colon and other parts of the intestine was also reduced by the treatment, as was the incidence of diarrhoea.

Effects on treatment on body weight

The beneficial effect of treatment with a hydrogel according to the invention was also evident from the data on body weight. The starting body weights for the control and the hydrogel treated groups did not differ significantly. However, one week after TNB administration, there was a significant weight loss in the untreated group (^a p=0.0008) whereas the group treated with the hydrogel of Example 7 showed a significant weight gain compared to the control group. The results are shown in Table 6.

Table 6

Type of Hydrogel	No. of animals	Weight [g]
Day 0 (i.e. initial weight)	10	218.0
Control=TNB	10	203.9 ^a
Example 5	10	207.8
Example 6	10	214.6
Example 7	10	220.1 ^b

^a p=0.0008^b p=0.0104

5

The best mode of performing the invention known to date, is to use a hydrogel according to Examples 1, 2 and 3.

Conclusion

10

The results presented above, clearly support that by using a hydrogel composition of the present invention, it is possible to treat ulcerative colitis without the need for also a local anaesthetic. This is advantageous from a side-effect point of view in the gastrointestinal body and in the CNS system.

15

Claims

1. Use of a hydrogel formulation consisting essentially of
- 5 (i) one or more gelling agents;
(ii) water;
(iii) optionally a pH-adjusting agent;
(iv) optionally a plasticizer; and
10 (v) optionally a surfactant;
- for the manufacture of a medicament for the treatment of distal inflammatory bowel diseases.
- 15 2. Use according to claim 1, for the rectal treatment of ulcerative colitis.
3. Use according to claim 1 or 2, wherein the gelling agent is selected from one or more of hydroxypropyl methylcellulose, Carbopol[®] (carbomer 934 (MF18)), pectin, sodium carboxymethylcellulose and agar.
- 20 4. Use according to claim 3, wherein the gelling agent is hydroxypropyl methylcellulose.
5. Use according to claim 3, wherein the gelling agent is agar.
- 25 6. Use according to any of the preceding claims, wherein the pH value of the formulation is within the range from 4.0 - 7.0.

7. A process for the preparation of a hydrogel composition of claim 1, whereby

(i) one or more gelling agents are mixed with water while stirring, optionally adding any other ingredients, the final weight of the composition is optionally adjusted with purified water, and the pH-value is finally adjusted with a suitable acid and/or base;

or

(ii) one or more gelling agents are mixed with water, the mixture is allowed to swell, whereafter any other ingredients are added and the final weight of the composition is adjusted.

8. A process according to claim 7, further comprising the step of filling the hydrogel composition into a syringe or vial, which thereafter is sealed and finally sterilized.

9. A syringe or vial comprising a hydrogel composition for use according to claim 1.

10. A method for the treatment of a subject suffering from distal inflammatory bowel disease, whereby a hydrogel formulation comprising

(i) one or more gelling agents;

(ii) water;

(iii) optionally a pH-adjusting agent;

(iv) optionally a plasticizer; and

(v) optionally a surfactant;

is administered to a subject in need of such treatment.

11. A method according to claim 10, for the rectal treatment of ulcerative colitis.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01122

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/00, A61K 47/38, A61K 47/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS, USPATFULL, WPI, CLAIMS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3930005 A (ROBERT WOJNAR ET AL), 30 December 1975 (30.12.75), column 2, line 38-46, example 29 --	1-11
X	GB 1552521 A (TOKO YAKUHI KOGYO KABUSHIKI KAISHA), 12 Sept 1979 (12.09.79), page 1, line 61-94 --	1-11
A	EP 0231040 A1 (AKZO N.V.), 5 August 1987 (05.08.87), page 3, line 1-30; page 5, line 19-25 --	1-11

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

<ul style="list-style-type: none"> * Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	<ul style="list-style-type: none"> "I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search 24 October 1997	Date of mailing of the international search report 05 - 11 - 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01122

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>Dialog Information Services, WPI, Dialog accession no. 009210300, WPI accession no. 92-337722/199241, Teikoku Seiyaku KK: "Intestinal injection preparations administered from anus into intestines - comprising main drug and agent to diffuse main drug which only becomes mixed on admin"; & JP,A,4244016, 19920901</p> <p style="text-align: center;">-- -----</p>	1-11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 97/01122

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 10-11 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/97

International application No.

PCT/SE 97/01122

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
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